PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| 47714-5001WO | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US99/15129 | 02/07/1999 | 02/07/1998 |
| International Patent Classification (IPC) or national classification and IPC<br>C12N15/10 | | |
| Applicant<br>RESEARCH AND DEVELOPMENT INSTITUTE, INC. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 31/01/2000 | 19.09.2000 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Wimmer, G<br>Telephone No. +49 89 2399 7347 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/15129

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-44 as originally filed

**Claims, No.:**

1-19 as originally filed

**Drawings, sheets:**

1/8-8/8 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | |
| | No: | Claims | 18 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-13, 19 |
| Industrial applicability (IA) | Yes: | Claims | |
| | No: | Claims | 14-17 |

2. Citations and explanations

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/15129

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability.**

The application does not meet the requirements of Art.33 PCT since claim **18 is not novel**, and **claims 1-13 and 19 do not appear to contain an inventive step.**

1. Reference is made to the following documents (the document numbering corresponds to their order of citation in the international search report):

   D1: JAVERZAT J.-P. ET AL.: 'Isolation of telomeric DNA from the filamentous fungus Podospora anserina and construction of a self-replicating linear plasmid showing high transformation frequency' NUCL. ACIDS RES., vol. 21, no. 3, 1993, pages 497-504, XP002124428

   D3: POWELL W.A. & KISTLER H.C.: 'In vivo rearrangement of foreign DNA by Fusarium oxysporum produces linear self-replicating plasmids' J. BACTERIOL., vol. 172, no. 6, 1906 - 1990, pages 3163-3171, XP000857613 cited in the application

   D4: GARCIA-PEDRAJAS M.D. & RONCERO M.I.: 'A homologous and self-replicating system for efficient transformation of Fusarium oxysporum' CURR. GENET., vol. 29, no. 2, January 1996 (1996-01), pages 191-198, XP000857612 cited in the application

   D5: National Science Foundation (USA), Grant No. 9724999 (Long D.M.) 'SGER: Efficient extrachromosomal replication of exogenous DNA by a filamentous fungus' (1997) http://fundedresearch.cos.com/cgi-bin/NSF/getRec?9724999 XP002124429 cited in the application

2. Document D1 describes the introduction of exogenous DNA into the deuteromycete *Podospora anserina*, its maintenance as linear extrachromosomal elements, and the addition of telomeric sequences to this DNA.

   Since *Podospora* is to-date classified as a deuteromycete (see also sect. VIII), the subject-matter of claim **18** is disclosed, and the claim therefore regarded not to be novel (Art. 33(2) PCT).

Since no prior art could be found describing introduction of DNA into Pestalotiopsis cells, the claims **1 - 13** and **19** are considered to be novel.

Claims **14 - 17** would be considered novel since neither the isolation of *Pestalotiopsis* telomerase nor of the nucleic acid encoding it have been described in the prior art; however these claims lack support by the description (see sect. VIII).

3. DNA transformation procedures and the resulting *in vivo* addition of telomere, giving rise to stable extrachromosomal DNA, have been described for a variety of fungi, e.g. *Podospora anserina* (D1) or *Fusarium oxysporum* (D3, D4). Regarding D3 as the closest prior art, the technical problem would be the provision of an alternative fungal species which, upon introduction of exogenous DNA, is capable of adding telomeres to said DNA, resulting in autonomously replicating DNA elements.

Document D5 describes the discovery that *Pestalotiopsis microspore*, unlike many other filamentous fungi, has the ability to convert non-replicating transforming DNA to self-replicating plasmids.

The person skilled in the art would therefore assume a similar principle for extrachromosomal plasmid maintenance in the genera *Pestalotiopsis* and *Fusarium*. Therefore, the combination of the teachings of the documents D3 and D5 would prompt the person skilled in the art to use the method of D3, and the genus *Pestalotiopsis* from D5 as a target cell. The claims **1-3** are therefore not considered to be inventive.

Claim **4** refers to a method of transformation, including the introduction of exogenous DNA into *Pestalotiopsis* cells, the addition of telomeric sequences to said DNA in those cells, the extraction of the extrachromosomal DNA from the cells, and the reintroduction of the modified DNA into a second cell.

Document D3 already states the isolation of extrachromosomal plasmid DNA produced in *Fusarium* cells, and the re-introduction into wild-type cells of the same

species, and into cells of other species (D3, pg. 3167). The technical problem is therefore again the provision of a species which can be used as an alternative to *Fusarium* for this method of transformation.

As stated above, a person skilled in the art would assume, reading document D5, similar principles of extrachromosomal DNA maintenance for *Fusarium* and *Pestalotiopsis*. The combination of the method described in D3 and the genus of D5 again would therefore result in the disclosure of claim 4, which is accordingly regarded as not being inventive.

The same applies to the dependent claims **5-13** and **19**, since none of these claims introduces any features with, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect to inventive step.

Claims **14 - 17** refer to *Pestalotiopsis* telomerase, a nucleic acid encoding this telomerase, host cells capable of expressing the telomerase, and the application of the telomerase for the creation of stable DNA elements by addition of telomeric repeats to DNA.
None of the prior art documents cited in here indicate the isolation of the telomerase gene or protein from the respective species. Furthermore, none of these documents suggest an *in vitro* treatment of DNA to arrive at DNA elements with the desired properties. Accordingly, present claims 14-17 are regarded as containing an inventive step.
However, it appears that support by the description is compromised (see also sect. VIII) in these claims.

**Re Item VIII**
**Certain observations on the international application**

The subject-matter of claim 14 is not clearly defined(Art. 6 PCT) as no sequence information is given for Pestalotiopsis telomerase. Similar reasoning applies to the dependent claim 15, and to claim 17.
Likewise, the subject-matter of claim 16 lacks support by the description, since the

isolation of the telomerase and its use in the claimed method have not been described.

The subject-matter of claim 18, which is defined using the classification "deuteromycetes" to describe the target cell, is unclear since the Deuteromycetes are an artificial category, combining species which appear to lack a sexual stage. However, it is generally accepted that the majority of the Deuteromycetes represent the nonsexual stage of sexually reproducing Ascomycetes and Basidiomycetes (see http://pollenuk.worc.ac.uk/Aero/Fungi/types.htm for expert opinion).